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# Synthesis of substituted *N*-hydroxyureas via the in situ generation of *t*-butoxy isocyanate

Josef G. Krause, Brian D. Leskiw, Michelle L. Emery, Megan E. McGahan, Mary P. McCourt, Ronny Priefer *

*Department of Chemistry, Biochemistry, and Physics, Niagara University, NY 14109, USA*

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ABSTRACT

Treatment of primary and secondary amines with *tert*-butylmesitylenesulfonoxycarbamate and a base afforded *tert*-butoxyurea, which when treated with an acid ultimately yielded substituted *N*-hydroxy ureas. It is proposed that this proceeded via the generation of *t*-butoxy isocyanate in situ. This method allows for the synthesis of both mono and disubstituted *N*-hydroxyureas.



In our quest to synthesize hydrazines for our antimicrobial study,[1] we explored the possible reaction of amines with *tert*-butylmesitylenesulfonoxycarbamate (**1**) to form the Boc-protected hydrazine carbamate, which when coupled with deprotection should ultimately yield the hydrazine. Based upon the amination work by Boger, Genêt, and Zheng on phenols,[2] boranes,[3] carbanions,[4] and enolates,[5] respectively, we felt encouraged that this route would be successful. The arenesulfonyloxycarbamates are relatively shelf stable and have also been used in intramolecular Sharpless aminohydroxylation reactions[6] as well as aziridination[7] on numerous alkenes, including fullerenes,[8] where a nitrene intermediate was proposed. When we attempted our synthesis, what we ultimately obtained was the N-substituted hydroxyurea, **2** (Fig. 1).

A Lossen-type rearrangement seemed to be the most likely mechanistic pathway (Scheme 1) whereby there is a base-induced deprotonation of the carbamate, simultaneous migration of the *t*-butoxy, and mesylsulfonyloxy removal.[9] This would generate the *t*-butoxy isocyanate (**3**) which is then attacked by the amine. This was previously observed by Bauer for the synthesis of ureas.[9] Genêt,[4a] Hanessian,[10] and Pellacani[11] have also proposed a similar mechanism with the use of other *tert*-butyl aryloxycarbamates, in the synthesis of hydroxamic esters and imidazolidin-2-ones, respectively.

As hydroxyureas have numerous biological uses, we further explored this synthetic path. *N*-hydroxyurea and many of its derivatives have been explored as possible antineoplastic agents,[12] used in the treatment of sickle cell anemia,[13] and are under investigation for the treatment of HIV.[14] In addition, they have also shown promise as hypoglycemic agents,[15] possible antimicrobial agents,[16], and have been shown to be a source of nitric oxide (NO).[17] The most common route for their synthesis is via isocyanate.[18] This however, will produce only mono-N-substituted hydroxyureas. Very few methods have been developed to obtain N,N-disubstituted hydroxyureas. One approach involves the initial synthesis of 1-(4-nitrophenol)-*N*-(*O*-benzylhydroxy)carbamate, reacting with various amines, followed by hydrogenation deprotection.[19] Synthesis of N,N-disubstituted carbamoyl chloride, via phosgene, and reaction with hydroxylamine;[16,20] reacting secondary amines with aryl-*N*-hydroxycarbamates;[21] as well as the use of triphosgene[22] have all shown limited but positive results. Since *t*-butoxy isocyanate that is generated in situ can be reacted with both primary as well as secondary amines, both mono and disubstituted hydroxyureas could be produced in this manner. We herein report our two-step procedure for obtaining hydroxyurea derivatives.

Although *tert*-butylmesitylenesulfonoxycarbamate (**1**) is commercially available, it is quite easily prepared from the *t*-butyl-*N*-hydroxycarbamate and 2-mesitylenesulfonyl chloride in nearly quantitative yields,[23] and can be used as it is without further purification. Initially we reacted **1** (1 equiv) with dibenzylamine (1 equiv) in DMF (1 M) with DBU (1 equiv) as a base. After an hour at 0 °C, ice water was added to the mixture which precipitated the *tert*-butoxyurea in 47% yield. We explored the use of different bases, and the highest yield was obtained with sodium hydride (Table 1, entry 3). Changes to other polar solvents (i.e., DMSO, MeOH, *t*-BuOH) did not enhance the yield. We therefore focused on NaH in DMF as our reaction condition. The cleavage of the *t*-butyl group to form the corresponding hydroxyurea was attempted with various acids. TFA, HI, HF, and $BF_3$ all gave yields that were significantly lower than those with HCl. Thus, we used 10 min reflux in conc HCl as our final deprotection step for all our compounds.

Numerous primary and secondary amines were used in this manner to synthesize substituted *N*-hydroxyureas (Table 2). Both

* Corresponding author. Tel.: +1 716 286 8261; fax: +1 716 286 8254.
*E-mail address:* rpriefer@niagara.edu (R. Priefer).

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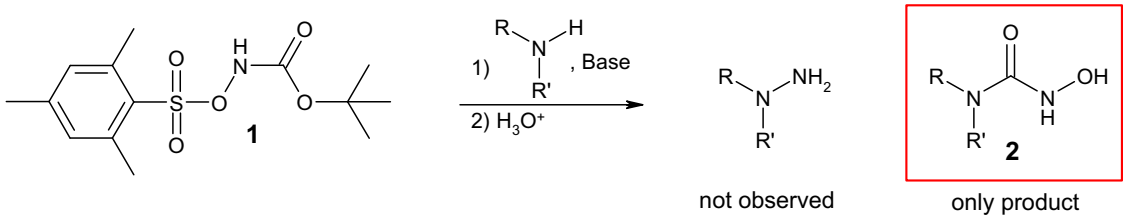
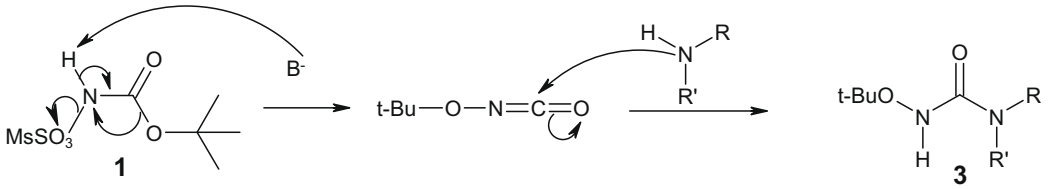



**Figure 1.** Hydroxyurea synthesis, **2**, from reacting amines with *tert*-butylmesitylenesulfonoxycarbamate (**1**).




**Scheme 1.** Proposed mechanism of hydroxyurea synthesis via a Lossen-type rearrangement.

the initial formation of the *tert*-butyl protected urea as well as the deprotection were successful in moderate to good yields. Aniline derivatives tended to give yields in the 60% range for the initial coupling (Table 2, entries 4–7). Best results were obtained with dibenzylamine, thus negating any steric concerns. What was interesting was when either 1-naphthylamine (**4**) or 1,4-dihydro-naphthalen-1,4-imine (**5**)[24] was used as the initial amine source, *N*-hydroxy-*N*′-1-naphthalenyl-urea (**6**) was obtained[25] (Table 2, entries 9 and 10, Fig. 2). Based upon NMR, the initial coupling to form the *tert*-butyl protected urea proceeded without incident. The aromatization of 1,4-dihydro-naphthalen-1,4-imine occurred during the deprotection with HCl to afford *N*-hydroxy-*N*′-1-naphthalenyl-urea (**6**).

**Table 1**
Yield of dibenzyl *tert*-butoxyurea with differing bases

| Entry # | Base | Yield (%) |
|---|---|---|
| 1 | DBU | 47 |
| 2 | DMAP | 60 |
| 3 | NaH | 84 |
| 4 | $NaOCH_3$ | 76 |
| 5 | KOH | 70 |
| 6 | KO*t*Bu | 50 |

**Table 2**
Yields of substituted *N*-hydroxyureas for both initially coupling and deprotection

| Entry | Amine | Yield of $R_1R_2NCONHOtBu$ (%) | Yield of $R_1R_2NCONHOH$ (%) |
|---|---|---|---|
| 1 | $C_6H_5CH_2NH_2$ | 45 | 90 |
| 2 | $(C_6H_5CH_2)NH$ | 85 | 70 |
| 3 | $C_6H_5CH_2NHCH_3$ | 59 | 43 |
| 4 | $C_6H_5CH_2NHC_6H_5$ | 65 | 63 |
| 5 | $C_6H_5NH_2$ | 62 | 65 |
| 6 | *p*-Cl-$C_6H_4NH_2$ | 67 | 68 |
| 7 | $C_6H_5NHCH_3$ | 60 | 55 |
| 8 | $C_6H_{11}NH_2$ | 58 | 53 |
| 9 | 1-Napthylamine | 84 | 92 |
| 10 | 1,4-Dihydro-naphthalen-1,4-imine | 81 | 86 |

In summary, this two-step procedure, via *t*-butoxy isocyanate, allows for the synthesis of both mono and disubstituted hydroxyureas in moderate to good yields. This novel method does have some major advantages over other techniques. The copious amounts of primary and secondary amines, as well as aniline derivatives, allows for numerous hydroxyureas to be synthesized. In addition, the common technique for synthesizing monosubstituted derivatives typically employs isocyanates, which have safety concerns. Finally, our method does not employ phosgene, which is also notoriously dangerous.

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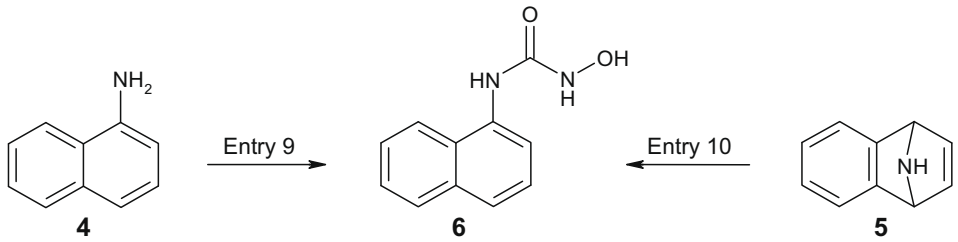


**Figure 2.** Synthesis of *N*-hydroxy-*N*′-1-naphthalenyl-urea (**6**) from both 1-naphthylamine (**4**) or 1,4-dihydro-naphthalen-1,4-imine (**5**).

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25. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 5.74 (s, 1H), 7.47 (t, $J$ = 8.0 Hz, 1H), 7.50–7.56 (m, 2H), 7.66 (d, $J$ = 6.8 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 1H), 7.90–7.94 (m, 2H), 8.85 (s, 1H), 8.98 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 120.8, 122.3, 124.6, 125.9, 126.0, 126.1, 128.0, 128.4, 133.9, 134.0, 159.5. Exact mass calculated for $C_{11}H_{10}O_2N_2$ 202.0737, found 202.07382.